

REMARKS/ARGUMENTS

With this response Applicants amend Claims 24 - 32 of the existing claims to correct typographical errors therein and to correct the dependencies thereof and request entry of new claims 34 - 52. Claims 3 - 5, 12 - 18 and 20 - 54 are presently under examination in this case.

Additional claim fees:

Applicants observe that the filing receipt in this matter indicates that fees were paid for three (3) independent claims and nineteen (19) total claims. The additional claims submitted herewith comprise five (5) independent claims and twenty-one (21) total claims. Fees for two (2) additional independent claims and for two (2) additional total claims and any other claims fees necessary for the claims listed herein are to be charged to deposit account 26-0166.

Support for subject matter of replacement claims:

Support for "non-hygroscopic" recited in new claim 35 can be found in the disclosure at page 3, lines 10 - 16 and in Figure 2.

Literal support for "physically stable" recited in new claim 35 can be found in the disclosure at page 2, line 18.

Literal support for "lubricant" recited in new claim 36 can be found in the disclosure at page 3, line 25 et seq.

New claims 46 to 49 are dependent on new claim 44 and are directed to a method of use of the pharmaceutical composition claimed in claim 42.

New claim 54 is a product by process claim.

Response:

The Examiner has rejected claims 3-5, 12-18 and 20-33 under 35 USC § 102(b) as being anticipated by Evenden *et al.*, WO 95/11891. Applicants respectfully traverse this rejection. Applicants point out that WO 95/11891 discloses the base compound by name at page 6, lines

20-21, but merely recites "compounds of the invention are . . . in the form of the free base or pharmaceutically acceptable salts thereof." WO 95/11891, at page 7, lines 1 - 4, recites that "organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable addition salts of the compounds of this invention." WO 95/11891 then recites forty-four (44) different illustrative acids including hydrochloric and tartaric acids. WO 95/11891 does not describe (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate salt. Accordingly, WO 95/11891 does not describe the subject matter of the claims of the present application and hence does not anticipate the present invention.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the present claims under 35 USC § 102(b).

The Examiner has rejected Claims 3-5, 12-15, 20-21 and 23-30 under 35 USC § 103 as being unpatentable over Evenden *et al.*, WO 95/11891 (page 3 of the Office action), and has rejected Claims 16-18, 22 and 31-33 under 35 USC § 103 as being unpatentable over the same reference (page 4 of the Office action). In view of the redrafting of the claims, Applicants respond to both rejections as follows.

The Examiner states, at page 3, "Evenden *et al.*, teach similar compounds having general formula I, . . . their organic and inorganic salts, . . . their pharmaceutical preparations (compositions) and method of use for the treatment of CNS disorders." The Examiner further states, at page 4, that Evenden *et al.*, "teach . . . a process of making their salts comprising adding ether solution of the compounds to a second ether solution of hydrochloric acid." and that "Evenden *et al.*, also teach that tartaric acid could be used to make the salts." Applicants respectfully traverse the rejection.

In order for an invention to be obvious, there must be suggestion or motivation in the prior art to make the invention. Here, one of ordinary skill in the art would have to be motivated by Evenden *et al.*, to choose the monohydrate (2*R*,3*R*)-tartrate salt over the numerous salts that could be made.

Applicants respectfully observe that Evenden *et al.*, list forty-four (44) different acids as illustrative examples that can be employed to form pharmaceutically acceptable salts with no guidance whatsoever that any one acid differs in any way from any other acid. Evenden *et al.*, state, "These salts are readily prepared by method known in the art." (page 7, lines 16-17). However, this is not to be read to indicate that other methods to prepare salts could not be discovered.

Evenden *et al.*, describe "dissolving the pure base in ether and dropping an excess of an ethereal HCl solution." (page 32, lines 10-12). Evenden *et al.*, do not describe dissolving the base in tetrahydrofuran, diluting the solution with diethyl ether, adding a solution of (2*R*,3*R*)-tartaric acid made by dissolving the acid in tetrahydrofuran and diluting with diethyl ether and recrystallizing the crystalline solid from 1.5% aqueous acetone as is described in the present application (page 7, Example 2). The Examiner has cited no art to suggest that this process is a process known in the art at the time this application was filed.

Evenden *et al.*, describe that forty-four acids are equivalent and that all can be used to form pharmaceutically acceptable salts of the base compounds. Furthermore, in all their examples, they only describe the formation of hydrochlorides; and in each Example merely state that the product is a white solid. Applicants can find no suggestion or motivation in Evenden *et al.*, to select any one of the forty-four acids over any other acid. Thus, Applicants respectfully submit that the disclosure of Evenden *et al.*, is no more than an invitation to experiment. Particularly, there is nothing in the disclosure of Evenden *et al.*, that suggests or that would motivate one of ordinary skill in the art to choose a particular acid, choose a particular enantiomer of the acid or use the process described in the instant application; and there is nothing in Evenden *et al.*, that suggests that that a chosen acid would yield a salt that was non-hygroscopic and that had good solubility and dissolution properties.

Applicants respectfully suggest that the disclosure of Evenden *et al.*, does not make the present invention *prima facie* obvious. Applicants suggest that Evenden *et al.*, provides, at most, only a suggestion to try a tartrate salt. But a suggestion to try something is not the test for obviousness. However, assuming only for arguments sake that the present invention is *prima*


facie obvious in view of Evenden *et al.*, Applicants respectfully submit that the instant application includes objective evidence of secondary considerations i.e., unexpected and surprising results, sufficient to rebut a *prima facie* case. Applicants respectfully request that the Examiner consider such objective criteria in making a determination of obviousness. Evidence of surprising and unexpected properties, for example stability, has been accepted by the patent office on numerous occasions to support patentability. The present specification discloses that the hydrochloride salt and the (2*R*,3*R*)-tartrate salt have very different properties. Figure 2 shows that in the monohydrate form of the tartrate salt, water is firmly bound in the crystal lattice and that the monohydrate (2*R*,3*R*)-tartrate does NOT absorb water with increased percent relative humidity up to 95 percent humidity. In contrast, Figure 2 also shows that the hydrochloride salt has very different properties; it readily absorbs water up to more than 20 percent by weight and is even deliquescent. The Examiner will appreciate that nothing in Evenden *et al.*, suggests these results or suggests that these two salts will have such different properties.

Conclusion:

In view of the amended and new claims submitted herewith and the above comments and remarks, Applicant respectfully submits that the invention described in the claims is patentable. Accordingly, Applicants earnestly request reconsideration and withdrawal of all rejections and allowance of the claims submitted herein.

Respectfully submitted,

Dated: September 11, 2003

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